Synthesis and Antiviral Evaluation of Sugar Uracil-1-ylmethylhydrazones and Their Oxadiazoline Derivatives

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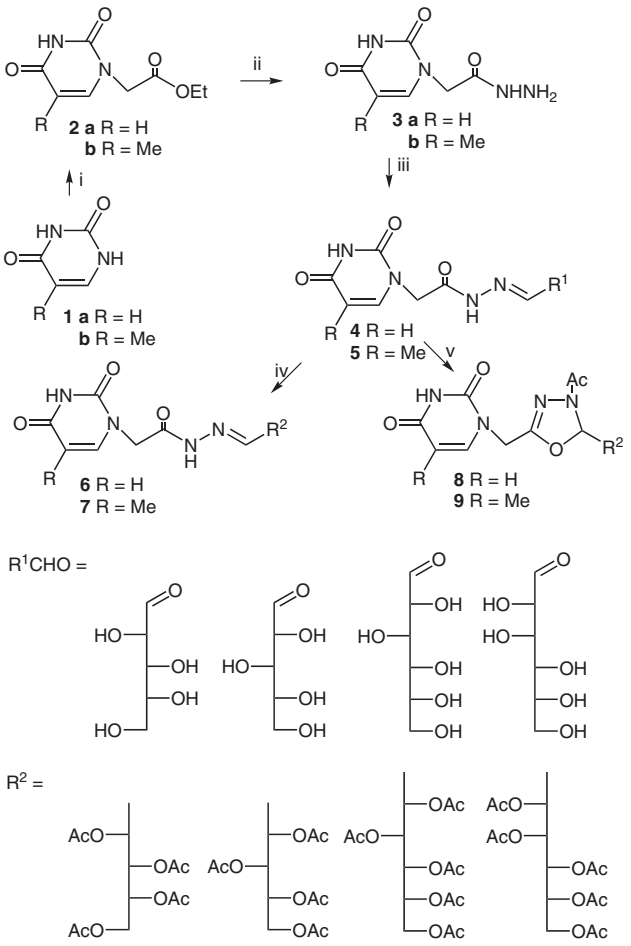
Abstract: 1-Carbethoxymethyluracils have been synthesized and derivatized to the corresponding hydrazides, which were reacted with monosaccharides to afford the corresponding sugar hydrazones. Acetylation of the latter with acetic anhydride in pyridine, afforded the per-*O*-acetyl derivatives, while heating in acetic anhydride gave the corresponding oxadiazolines. The prepared compounds were tested for antiviral activity against hepatitis B virus and showed moderate activities.

Key words: antiviral agents, carbohydrates, hydrazones, nucleobases, nucleosides

1,3,4-Oxadiazoles and 1,3,4-oxadiazolines have been the subject of chemical and biological studies on account of their interesting pharmacological properties; they possess antimicrobial, anti-inflammatory, analgesic and anti-tumor activities.[1] In addition, several 1,3,4-oxadiazole and 1,3,4-oxadiazoline derivatives have been reported to possess diverse biological activities[2] as well as antiviral activity against HIV[3] and tyrosinase inhibiting effects.[4] Although there are numerous antibiotics that are commercially used in medicine, the synthesis of new compounds is of vital importance due to increasing drug resistance. Moreover, it is important to obtain therapeutical compounds with less toxic effects. A number of syntheses for substituted derivatives of these heterocyclic systems have been developed, in particular, C-nucleosides bearing five-membered nitrogen heterocycles such as tiazofurin,[5] selenazofurin[6] and showdomycin[7] have been shown to possess a wide range of medicinal properties, including antibiotic, antiviral and anti-tumor activity. Recently, the synthesis of acyclonucleosides has attracted much attention.[8] As a consequence of the above significance and possible enhancement of biological activity resulting from the attachment of carbohydrate moieties to 1,3,4-oxadiazoline heterocycles, together with our interest in the synthesis of heterocyclic derivatives of carbohydrates,[9] our attention was drawn to the synthesis of oxadiazoline derivatives using monosaccharide 1-acetylhydrazinouracils.

Uracil derivatives **1a** and **1b** were allowed to react with ethyl chloroacetate in acetone and anhydrous potassium carbonate, to afford 1-carbethoxymethyluracils **2a** and **2b**, respectively. Hydrazinolysis of the ethyl ester group was carried out in ethanol under reflux, to afford the corresponding hydrazides **3a** and **3b**, respectively, in 90–93% yields. Reaction of the latter hydrazides with equimolar amounts of a range of monosaccharides was performed by heating an aqueous ethanolic solution in the presence of a catalytic amount of acetic acid. Hydrazones **4** and **5** were prepared from the monosaccharides L-arabinose, D-xylose, D-glucose and D-mannose. The ^{1}H NMR spectra of the hydrazones **4** and **5** confirmed the presence of sugar protons, which gave signals in the range δ = 3.25–4.10 ppm and anomeric protons in the region δ = 7.44–7.55 ppm (Table 1). Assignment of the sugar protons was based on the chemical shift equivalencies to the assigned structure of other related sugar hydrazones.[9,10]



Scheme 1 *Reagents and conditions*: i) $ClCH_2CO_2Et$, K_2CO_3, acetone, reflux, 3 h, 85–89%; ii) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 4 h, 90–93%; iii) R^1CHO, EtOH, AcOH, reflux, 5 h, 88–95%; iv) Ac_2O, Py, r.t., overnight, 95–99%; v) Ac_2O, reflux, 1 h, 68–71%.

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Table 1 Mass, ^{1}H and ^{13}C NMR Spectra of Newly Synthesized Compounds

Compd	*m/z* [M$^+$]	^{1}H NMR (DMSO-d_6)	^{13}C NMR (DMSO-d_6)
2a	198	1.20 (t, *J* = 8.1 Hz, 3 H, CH_3CH$_2$), 4.19 (q, *J* = 8.1 Hz, 2 H, CH$_3$CH_2), 4.61 (s, 2 H, CH$_2$), 6.50 (d, *J* = 5.5 Hz, 1 H, H-5), 8.28 (d, *J* = 5.5 Hz, 1 H, H-6), 10.81 (br s, 1 H, NH).	14.0 (*C*H$_3$CH$_2$O), 46.1 (CH$_2$), 61.4 (CH$_3$*C*H$_2$O), 101.1 (C-5), 142.5 (C-6), 150.9 (C-2), 163.9 (C-4), 166.9 (C=O).
2b	212	1.19 (t, *J* = 8.1 Hz, 3 H, CH_3CH$_2$), 2.11 (s, 3 H, CH$_3$), 4.17 (q, *J* = 8.1 Hz, 2 H, CH$_3$CH_2), 4.61 (s, 2 H, CH$_2$), 8.10 (s, 1 H, H-6), 11.09 (br s, 1 H, NH).	11.9 (CH$_3$), 14.1 (*C*H$_3$CH$_2$O), 46.3 (CH$_2$), 61.6 (CH$_3$*C*H$_2$O), 111.1 (C-5), 137.5 (C-6), 151.4 (C-2), 164.4 (C-4), 166.7 (C=O).
3a	184	4.20 (br s, 2 H, NH$_2$), 4.63 (s, 2 H, CH$_2$), 6.80 (d, *J* = 5.5 Hz, 1 H, H-5), 8.05 (d, *J* = 5.5 Hz, 1 H, H-6), 9.55 (br s, 1 H, NH), 11.22 (br s, 1 H, NH).	51.3 (CH$_2$), 101.7 (C-5), 143.7 (C-6), 151.7 (C-2), 164.2 (C-4), 168.4 (C=O).
3b	198	2.01 (s, 3 H, CH$_3$), 4.22 (br s, 2 H, NH$_2$), 4.63 (s, 2 H, CH$_2$), 8.19 (s, 1 H, H-6), 9.60 (br s, 1 H, NH), 10.81 (br s, 1 H, NH).	12.1 (CH$_3$), 51.9 (CH$_2$), 110.8 (C-5), 137.9 (C-6), 150.6 (C-2), 163.9 (C-4), 168.7 (C=O).
4a	317	3.35–3.58 (m, 4 H, H-3′, H-4′, H-5′), 3.65 (m, 1 H, H-2′), 4.39 (br s, 1 H, OH), 4.60 (br s, 1 H, OH), 4.63 (s, 2 H, CH$_2$), 4.78 (br s, 1 H, OH), 5.11 (br s, 1 H, OH), 6.78 (d, *J* = 5.5 Hz, 1 H, H-5), 7.55 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.40 (d, *J* = 5.5 Hz, 1 H, H-6), 11.20 (br s, 1 H, NH), 12.18 (br s, 1 H, NH).	53.4 (CH$_2$), 63.0 (C-5′), 69.2 (C-4′), 75.7 (C-2′), 76.6 (C-3′), 102.6 (C-5), 141.7 (C-6), 149.4 (C-1′), 150.2 (C-2), 163.8 (C-4), 167.5 (C=O).
4b	317	3.25–3.57 (m, 5 H, H-2′, H-3′, H-4′, H-5′), 4.30 (br s, 1 H, OH), 4.50 (br s, 2 H, 2 × OH), 4.63 (s, 2 H, CH$_2$), 5.20 (br s, 1 H, OH), 6.78 (d, *J* = 5.5 Hz, 1 H, H-5), 7.50 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.28 (d, *J* = 5.5 Hz, 1 H, H-6), 11.20 (br s, 1 H, NH), 12.00 (br s, 1 H, NH).	53.2 (CH$_2$), 62.9 (C-5′), 69.3 (C-4′), 75.4 (C-2′), 76.9 (C-3′), 101.9 (C-5), 141.1 (C-6), 148.1 (C-1′), 149.4 (C-2), 163.2 (C-4), 166.2 (C=O).
4c	346	3.28–3.92 (m, 5 H, H-3′, H-4′, H-5′, H-6′), 4.10 (m, 1 H, H-2′), 4.40 (br s, 1 H, OH), 4.60 (br s, 2 H, 2 × OH), 4.63 (s, 2 H, CH$_2$), 5.02 (br s, 1 H, OH), 5.40 (br s, 1 H, OH), 6.90 (d, *J* = 5.5 Hz, 1 H, H-5), 7.48 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.30 (d, *J* = 5.5 Hz, 1 H, H-6), 11.00 (br s, 1 H, NH), 11.60 (br s, 1 H, NH).	53.3 (CH$_2$), 62.9 (C-6′), 69.0 (C-4′), 70.0 (C-5′), 73.0 (C-2′), 73.4 (C-3′), 101.6 (C-5), 141.0 (C-6), 149.9 (C-1′), 150.3 (C-2), 163.0 (C-4), 169.9 (C=O).
4d	346	3.27–4.05 (m, 6 H, H-2′, H-3′, H-4′, H-5′, H-6′), 4.63 (s, 2 H, CH$_2$), 4.78 (br s, 1 H, OH), 6.60 (d, *J* = 5.5 Hz, 1 H, H-5), 7.46 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.20 (d, *J* = 5.5 Hz, 1 H, H-6), 10.40 (br s, 1 H, NH), 11.08 (br s, 1 H, NH).	53.5 (CH$_2$), 62.4 (C-6′), 68.3 (C-4′), 69.7 (C-5′), 71.6 (C-2′), 72.5 (C-3′), 101.7 (C-5), 140.4 (C-6), 147.3 (C-1′), 150.1 (C-2), 163.3 (C-4), 170.0 (C=O).
5a	330	2.08 (s, 3 H, CH$_3$), 3.38–3.55 (m, 4 H, H-3′, H-4′, H-5′), 3.67 (m, 1 H, H-2′), 4.40 (br s, 1 H, OH), 4.61 (br s, 1 H, OH), 4.63 (s, 2 H, CH$_2$), 4.75 (br s, 1 H, OH), 5.16 (br s, 1 H, OH), 7.50 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.21 (s, 1 H, H-6), 11.19 (br s, 1 H, NH), 12.18 (br s, 1 H, NH).	12.6 (CH$_3$), 52.7 (CH$_2$), 62.4 (C-5′), 67.2 (C-4′), 70.5 (C-2′), 71.9 (C-3′), 111.2 (C-5), 138.0 (C-6), 146.2 (C-1′), 150.0 (C-2), 164.0 (C-4), 166.7 (C=O).
5b	330	2.02 (s, 3 H, CH$_3$), 3.30–3.60 (m, 5 H, H-2′, H-3′, H-4′, H-5′), 4.30 (br s, 1 H, OH), 4.58 (br s, 2 H, 2 × OH), 4.63 (s, 2 H, CH$_2$), 5.20 (br s, 1 H, OH), 7.45 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.18 (s, 1 H, H-6), 11.20 (br s, 1 H, NH), 12.09 (br s, 1 H, NH).	11.9 (CH$_3$), 52.9 (CH$_2$), 62.3 (C-5′), 68.6 (C-4′), 73.0 (C-2′), 74.3 (C-3′), 111.0 (C-5), 137.7 (C-6), 147.3 (C-1′), 150.1 (C-2), 163.0 (C-4), 167.7 (C=O).
5c	360	2.06 (s, 3 H, CH$_3$), 3.25–3.45 (m, 5 H, H-3′, H-4′, H-5′, H-6′), 3.70 (m, 1 H, H-2′), 4.00 (br s, 1 H, OH), 4.18 (br s, 2 H, 2 × OH), 4.60 (br s, 1 H, OH), 4.63 (s, 2 H, CH$_2$), 4.92 (br s, 1 H, OH), 7.48 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.20 (s, 1 H, H-6), 10.50 (br s, 1 H, NH), 11.18 (br s, 1 H, NH).	12.2 (CH$_3$), 53.5 (CH$_2$), 62.5 (C-6′), 68.1 (C-4′), 72.0 (C-5′), 72.9 (C-2′), 73.7 (C-3′), 111.2 (C-5), 137.7 (C-6), 148.3 (C-1′), 150.4 (C-2), 162.5 (C-4), 167.4 (C=O).
5d	360	2.02 (s, 3 H, CH$_3$), 3.25–3.45 (m, 5 H, H-3′, H-4′, H-5′, H-6′), 3.70 (m, 1 H, H-2′), 3.80 (br s, 3 H, 3 × OH), 3.90 (br s, 1 H, OH), 4.45 (br s, 1 H, OH), 4.63 (s, 2 H, CH$_2$), 7.44 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.22 (s, 1 H, H-6), 10.11 (br s, 1 H, NH), 10.80 (br s, 1 H, NH).	12.1 (CH$_3$), 53.5 (CH$_2$), 62.4 (C-6′), 68.3 (C-4′), 69.7 (C-5′), 71.6 (C-2′), 72.5 (C-3′), 101.7 (C-5), 140.4 (C-6), 147.3 (C-1′), 150.1 (C-2), 163.3 (C-4), 170.0 (C=O).
6a	485[a]	1.95, 2.04, 2.10, 2.13, (4 × s, 12 H, 4 × CH$_3$CO), 4.17 (m, 2 H, H-5′), 4.25 (m, 1 H, H-4′), 4.50 (s, 2 H, CH$_2$), 5.60 (m, 1 H, H-3′), 5.75 (m, 1 H, H-2′), 6.61 (d, *J* = 5.5 Hz, 1 H, H-5), 7.26 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.25 (d, *J* = 5.5 Hz, 1 H, H-6), 10.10 (br s, 1 H, NH), 11.04 (br s, 1 H, NH).	20.4, 20.6, 21.0, 21.3 (4 × *C*H$_3$CO), 53.0 (CH$_2$), 58.0 (C-5′), 67.2 (C-4′), 71.7 (C-2′), 73.3 (C-3′), 103.2 (C-5), 140.4 (C-1′), 146.7 (C-6), 149.6 (C-2), 164.3 (C-4), 167.4, 167.9, 168.6, 169.5, 169.9 (5 × C=O).
6b	485[a]	1.96, 2.04, 2.09, 2.12, (4 × s, 12 H, 4 × CH$_3$CO), 4.15 (m, 2 H, H-5′), 4.23 (m, 1 H, H-4′), 4.48 (s, 2 H, CH$_2$), 5.61 (m, 1 H, H-3′), 5.70 (m, 1 H, H-2′), 6.62 (d, *J* = 5.5 Hz, 1 H, H-5), 7.27 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.22 (d, *J* = 5.5 Hz, 1 H, H-6), 10.08 (br s, 1 H, NH), 11.05 (br s, 1 H, NH).	20.7, 20.9, 21.1, 21.3 (4 × *C*H$_3$CO), 52.7 (CH$_2$), 58.2 (C-5′), 66.3 (C-4′), 71.6 (C-2′), 73.6 (C-3′), 102.3 (C-5), 140.8 (C-1′), 141.4 (C-6), 149.3 (C-2), 162.6 (C-4), 166.5, 166.9, 168.0, 169.2, 169.7 (5 × C=O).

Table 1 Mass, ^{1}H and ^{13}C NMR Spectra of Newly Synthesized Compounds (continued)

Compd	*m/z* [M$^+$]	^{1}H NMR (DMSO-d_6)	^{13}C NMR (DMSO-d_6)
6c	557[a]	1.95, 2.04, 2.10, 2.13, 2.15 (5 × s, 15 H, 5× CH_3CO), 4.00–4.11 (m, 2 H, H-6′), 4.50 (m, 1 H, H-5′), 4.60 (s, 2 H, CH_2), 4.70 (m, 1 H, H-4′), 5.15 (m, 1 H, H-3′), 5.45 (m, 1 H, H-2′), 6.61 (d, *J* = 5.5 Hz, 1 H, H-5), 7.27 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.23 (d, *J* = 5.5 Hz, 1 H, H-6), 10.06 (br s, 1 H, NH), 11.03 (br s, 1 H, NH).	20.5, 20.6, 20.8, 20.9, 21.3 (5 × *C*H_3CO), 53.5 (CH_2), 61.9 (C-6′), 65.5 (C-5′), 67.5 (C-4′), 72.0 (C-2′), 73.1 (C-3′), 102.9 (C-5), 140.7 (C-6), 141.5 (C-1′), 150.0 (C-2), 162.7 (C-4), 167.4, 168.0, 168.2, 168.5, 169.5, 169.9 (6 × C=O).
6d	557[a]	1.95, 2.04, 2.10, 2.13, 2.15 (5 × s, 15 H, 5 × CH_3CO), 4.06 (m, 2 H, H-6′), 4.40 (m, 1 H, H-5′), 4.60 (s, 2 H, CH_2), 4.68 (m, 1 H, H-4′), 5.15 (m, 1 H, H-3′), 5.50 (m, 1 H, H-2′), 6.62 (d, *J* = 5.5 Hz, 1 H, H-5), 7.28 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.20 (d, *J* = 5.5 Hz, 1 H, H-6), 10.10 (br s, 1 H, NH), 11.08 (br s, 1 H, NH).	20.2, 20.4, 20.6, 21.0, 21.2 (5 × *C*H_3CO), 52.1 (CH_2), 62.0 (C-6′), 65.5 (C-5′), 67.2 (C-4′), 71.4 (C-2′), 72.9 (C-3′), 101.9 (C-5), 140.0 (C-6), 141.4 (C-1′), 150.4 (C-2), 163.0 (C-4), 167.9, 168.0, 168.5, 169.0, 169.6, 170.0 (6 × C=O).
7a	499[a]	1.95, 2.04, 2.08, 2.10, 2.13 (5 × s, 15 H, 4 × CH_3CO, CH_3), 4.17 (m, 2 H, H-5′), 4.26 (m, 1 H, H-4′), 4.49 (s, 2 H, CH_2), 5.64 (m, 1 H, H-3′), 5.71 (m, 1 H, H-2′), 7.27 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.21 (s, 1 H, H-6), 10.05 (br s, 1 H, NH), 11.05 (br s, 1 H, NH).	12.2 (CH_3), 20.2, 20.4, 21.1, 21.3 (4 × *C*H_3CO), 53.9 (CH_2), 57.9 (C-5′), 67.3 (C-4′), 71.5 (C-2′), 73.6 (C-3′), 111.8 (C-5), 138.3 (C-6), 141.3 (C-1′), 148.9 (C-2), 164.2 (C-4), 167.3, 167.7, 168.1, 168.5, 169.5 (5 × C=O).
7b	499[a]	1.95, 2.04, 2.08, 2.10, 2.13 (5 × s, 15 H, 4 × CH_3CO, CH_3), 4.20 (m, 2 H, H-5′), 4.29 (m, 1 H, H-4′), 4.51 (s, 2 H, CH_2), 5.67 (m, 1 H, H-3′), 5.76 (m, 1 H, H-2′), 7.29 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.18 (s, 1 H, H-6), 10.06 (br s, 1 H, NH), 11.01 (br s, 1 H, NH).	12.1 (CH_3), 20.2, 20.5, 21.0, 21.4 (4 × *C*H_3CO), 53.4 (CH_2), 58.0 (C-5′), 67.6 (C-4′), 71.8 (C-2′), 73.7 (C-3′), 111.9 (C-5), 137.9 (C-6), 141.5 (C-1′), 150.0 (C-2), 163.9 (C-4), 167.7, 167.9, 168.1, 168.9, 170.1 (5 × C=O).
7c	571[a]	1.95, 2.04, 2.08, 2.10, 2.13, 2.15 (6 × s, 18 H, 5 × CH_3CO, CH_3), 4.03–4.12 (m, 2 H, H-6′), 4.48 (m, 1 H, H-5′), 4.68 (s, 2 H, CH_2), 4.72 (m, 1 H, H-4′), 5.21 (m, 1 H, H-3′), 5.50 (m, 1 H, H-2′), 7.31 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.21 (s, 1 H, H-6), 10.09 (br s, 1 H, NH), 11.03 (br s, 1 H, NH).	12.1 (CH_3), 20.4, 20.6, 21.0, 21.1, 21.3 (5 × *C*H_3CO), 53.2 (CH_2), 61.7 (C-6′), 65.6 (C-5′), 67.4 (C-4′), 71.9 (C-2′), 72.9 (C-3′), 111.3 (C-5), 137.9 (C-6), 141.8 (C-1′), 150.0 (C-2), 162.8 (C-4), 167.2, 168.0, 168.3, 168.9, 169.3, 170.1 (6 × C=O).
7d	571[a]	1.95, 2.04, 2.08, 2.10, 2.13, 2.15 (6 × s, 18 H, 5 × CH_3CO, CH_3), 4.09 (m, 2 H, H-6′), 4.46 (m, 1 H, H-5′), 4.69 (s, 2 H, CH_2), 4.70 (m, 1 H, H-4′), 5.18 (m, 1 H, H-3′), 5.51 (m, 1 H, H-2′), 7.30 (d, *J* = 2.5 Hz, 1 H, H-1′), 8.22 (s, 1 H, H-6), 10.10 (br s, 1 H, NH), 11.00 (br s, 1 H, NH).	12.2 (CH_3), 20.4, 20.6, 21.0, 21.2, 21.3 (5 × *C*H_3CO), 53.6 (CH_2), 62.0 (C-6′), 66.3 (C-5′), 67.6 (C-4′), 71.9 (C-2′), 72.9 (C-3′), 101.9 (C-5), 140.0 (C-6), 141.9 (C-1′), 150.0 (C-2), 163.1 (C-4), 167.6, 167.9, 168.1, 168.8, 169.4, 170.1 (6 × C=O).
8c	599[a]	1.80, 1.99, 2.02, 2.06, 2.15, 2.35 (6 × s, 18 H, 6 × CH_3CO), 3.87 (dd, *J* = 2.5, 8.5 Hz, 1 H, H-5′), 4.20 (dd, *J* = 2.5, 6.5 Hz, 1 H, H-5″), 4.39 (dd, *J* = 2.5, 6.5 Hz, 2 H, H-4′), 4.50 (s, 2 H, CH_2), 5.19 (m, 1 H, H-3′), 5.40 (dd, *J* = 3.5, 5.8 Hz, 1 H, H-2′), 5.58 (t, *J* = 5.8 Hz, 1 H, H-1′), 5.81 (d, *J* = 5.8 Hz, 1 H, oxadiazoline-H), 6.67 (d, *J* = 5.5 Hz, 1 H, H-5), 8.25 (d, *J* = 5.5 Hz, 1 H, H-6), 11.00 (br s, 1 H, NH).	20.4, 20.6, 20.8, 21.0, 21.1, 21.9 (6 × *C*H_3CO), 46.5 (CH_2), 62.1 (C-5′), 64.1 (C-3′), 65.6 (C-4′), 66.1 (C-2′), 67.9 (C-1′), 87.0 (C-2″, oxadiazoline), 101.6 (C-5), 143.1 (C-6), 149.6 (C-2), 159.7 (C-5″, oxadiazoline), 165.4 (C-4), 168.4, 168.9, 169.1, 169.4, 169.9, 171.2 (6 × CH_3*C*O).
8d	599[a]	1.90, 2.01, 2.07, 2.10, 2.15, 2.46 (6 × s, 18 H, 6 × CH_3CO), 4.09 (m, 1 H, H-5′), 4.30 (dd, *J* = 2.4, 6.5 Hz, 1 H, H-5″), 4.53 (s, 2 H, CH_2), 4.77 (m, 1 H, H-4′), 5.19 (m, 1 H, H-3′), 5.39 (m, 1 H, H-2′), 5.50 (dd, *J* = 2.5, 5.8 Hz, 1 H, H-1′), 5.80 (d, *J* = 5.8 Hz, 1 H, oxadiazoline-H), 6.65 (d, *J* = 5.5 Hz, 1 H, H-5), 8.25 (d, *J* = 5.5 Hz, 1 H, H-6), 11.02 (br s, 1 H, NH).	20.2, 20.6, 20.9, 21.1, 21.5, 21.9 (6 × *C*H_3CO), 46.7 (CH_2), 62.4 (C-5′), 64.7 (C-3′), 65.9 (C-4′), 66.2 (C-2′), 68.1 (C-1′), 87.4 (C-2″, oxadiazoline), 102.3 (C-5), 143.0 (C-6), 149.1 (C-2), 160.2 (C-5″, oxadiazoline), 163.2 (C-4), 168.3, 168.5, 169.3, 169.5, 169.9, 171.1 (6 × CH_3*C*O).
9c	613[a]	1.84, 1.99, 2.08, 2.13, 2.15, 2.38, 2.43 (7 × s, 21 H, 6 × CH_3CO, CH_3), 3.95(dd, *J* = 2.5, 8.5 Hz, 1 H, H-5′), 4.10 (dd, *J* = 2.5, 6.5 Hz, 1 H, H-5″), 4.40 (dd, *J* = 2.8, 6.5 Hz, 2 H, H-4′), 4.51 (s, 2 H, CH_2), 5.22 (m, 1 H, H-3′), 5.43 (dd, *J* = 3.5, 5.8, Hz, 1 H, H-2′), 5.60 (t, *J* = 5.8 Hz, 1 H, H-1′), 5.85 (d, *J* = 5.8 Hz, 1 H, oxadiazoline-H), 8.26 (s, 1 H, H-6), 11.02 (br s, 1 H, NH).	12.2 (CH_3), 20.1, 20.5, 20.7, 21.1, 21.4, 21.8 (6 × *C*H_3CO), 47.3 (CH_2), 62.2 (C-5′), 64.3 (C-3′), 65.9 (C-4′), 66.3 (C-2′), 68.4 (C-1′), 86.7 (C-2″, oxadiazoline), 111.2 (C-5), 138.5 (C-6), 150.2 (C-2), 159.9 (C-5″, oxadiazoline), 164.3 (C-4), 168.2, 168.6, 169.3, 169.5, 169.9, 171.3 (6 × CH_3*C*O).
9d	613[a]	1.93, 2.07, 2.11, 2.14, 2.17, 2.46, 2.50 (7 × s, 21 H, 6 × CH_3CO, CH_3), 4.17 (m, 1 H, H-5′), 4.38 (dd, *J* = 2.5, 6.5 Hz, 1 H, H-5″), 4.51 (s, 2 H, CH_2), 4.75 (m, 1 H, H-4′), 5.23 (m, 1 H, H-3′), 5.44 (m, 1 H, H-2′), 5.54 (dd, *J* = 2.5, 5.8 Hz, 1 H, H-1′), 5.81 (d, *J* = 5.8 Hz, 1 H, oxadiazoline-H), 8.23 (s, 1 H, H-6), 11.06 (br s, 1 H, NH).	12.3 (CH_3), 20.1, 20.4, 20.8, 21.3, 21.5, 21.8 (6 × *C*H_3CO), 47.5 (CH_2), 62.3 (C-5′), 64.5 (C-3′), 66.1 (C-4′), 66.9 (C-2′), 68.7 (C-1′), 86.9 (C-2″, oxadiazoline), 111.3 (C-5), 138.7 (C-6), 150.0 (C-2), 160.0 (C-5″, oxadiazoline), 164.0 (C-4), 168.2, 168.5, 169.4, 169.7, 169.9, 171.4 (6 × CH_3*C*O).

[a] MS-FAB [M$^+$ + 1].

Table 2 Structural Data of Compounds **4–9**

Compd	R	R^1CHO	R^2
4a	H	L-arabinose	–
4b	H	D-xylose	–
4c	H	D-glucose	–
4d	H	D-mannose	–
5a	Me	L-arabinose	–
5b	Me	D-xylose	–
5c	Me	D-glucose	–
5d	Me	D-mannose	–
6a	H	–	tetra-*O*-acetyl-L-arabinotetritolyl
6b	H	–	tetra-*O*-acetyl-D-xylotetritolyl
6c	H	–	penta-*O*-acetyl-D-glucopentitolyl
6d	H	–	penta-*O*-acetyl-D-mannopentitolyl
7a	Me	–	tetra-*O*-acetyl-L-arabinotetritolyl
7b	Me	–	tetra-*O*-acetyl-D-xylotetritolyl
7c	Me	–	penta-*O*-acetyl-D-glucopentitolyl
7d	Me	–	penta-*O*-acetyl-D-mannopentitolyl
8c	H	–	penta-*O*-acetyl-D-glucopentitolyl
8d	H	–	penta-*O*-acetyl-D-mannopentitolyl
9c	Me	–	penta-*O*-acetyl-D-glucopentitolyl
9d	Me	–	penta-*O*-acetyl-D-mannopentitolyl

For structural data of compounds **2–9**, see Table 2. Acetylation of sugar uracil-1-ylmethylhydrazones **4** and **5** gave differing products depending on the conditions of acetylation.[11] Thus, acetylation of compounds **4** and **5** with acetic anhydride in pyridine at room temperature, afforded the per-*O*-acetyl derivatives **6** and **7**. The ^{1}H NMR spectra of the latter showed the *O*-acetyl methyl groups at d = 1.95–2.15 ppm and the methine proton as a doublet at d = 7.26–7.31 ppm (Table 1). When the sugar hydrazones **4** and **5** were heated in acetic anhydride, the corresponding oxadiazoline derivatives **8** and **9** were obtained. The spectral data of these compounds were in agreement with the assigned structures, with the ^{1}H NMR spectra showing the acetyl methyl groups at d = 1.80–2.46 ppm. Elemental analyses of these compounds (Table 3) were in agreement with the assigned structures, confirming that, in addition to acetylation of the sugar hydroxyl groups, N-acetylation had also taken place (Scheme 1).

Preliminary viral screening against HBV (Hep G2 2.2.15 cell method),[12] indicated that compounds **5c**, **5d**, **6c**, **6d**, **7a–d**, **8c**, **8d**, **9c** and **9d** were found to be active against HBV replication with IC_{50} = ~79–94 μM and CC_{50} = ~85–95 μM, while compounds **4a–d**, **5a**, **5b**, **6a** and **6b** showed moderate viral replication inhibition and moderate cytotoxicity. The drug Lamivudine, which is a potent selective inhibitor of HBV replication,[13] was used as a standard for the comparative studies.

In conclusion, a number of sugar uracil-1-ylmethylhydrazones, O-acetylated derivatives of sugar uracil-1-ylmethylhydrazones and 4-acetyl-5-(*O*-acetylalditolyl)-2-(uracil-1-ylmethyl)-1,3,4-oxadiazolines were prepared. Some of these were tested for antiviral activity against Hepatitis-B virus (HBV, Hep G2 2.2.15 cell method). Structure activity correlation of the obtained results revealed that O-acetylated derivatives **6a**, **6d** and **7a–d**, followed by compounds **8c**, **8d**, **9c** and **9d**, in which the 1,3,4-oxadiazoline ring is attached to the O-acetylated sugar moiety, showed higher activity against HBV than did the deprotected sugar hydrazones.

Melting points were determined using a Kofler block instrument and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker AC 250 FT NMR spectrometer at 250 MHz. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. EIMS and FABMS spectra were recorded with a Finnigen MAT 312/AMD. Elemental analyses were performed at the microanalytical unit, Cairo University, Egypt. TLC analyses were conducted on silica gel Merck $60F_{254}$ coated on aluminum sheets. The detection was achieved by treatment with a solution of 15% H_2SO_4 in MeOH and heating at 150 °C. All reactions requiring anhydrous conditions were conducted in dried apparatus. All commercially available reagents were used without further purification. Pyridine was distilled from CaH_2 and stored over molecular sieves. Concentrations were carried out on a rotary evaporator at a temperature below 40 °C. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Shebin El-Koam, Egypt.

1-Carbethoxymethyluracils 2a,b; General Procedure

A mixture of uracil derivatives **1a**,**b** (0.1 mole), anhydrous acetone (300 mL), anhydrous K_2CO_3 (85.0 g, 0.6 mole) and ethyl chloroacetate (16.0 g, 0.13 mole) was heated under reflux for 3 h (monitored by TLC). The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized from EtOH to afford **2a**,**b** as colorless needles in 85–89% yields.

1-Acetylhydrazinouracils 3a,b; General Procedure

A mixture of **2a,b** (0.1 mole), hydrazine hydrate (10 mL) and MeOH (20 mL) was heated under reflux for 4 h. The product was filtered off and recrystallized from MeOH to give **3a**,**b** as colorless needles in 90–93% yields.

Sugar Uracil-1-ylmethyl Hydrazones 4–5; General Procedure

To a well stirred solution of the respective monosaccharide (2.80 mmol) and glacial AcOH (0.6 mL) in H_2O (15 mL), was added the appropriate 1-acetylhydrazinouracils **3a**,**b** (2.80 mmol) in EtOH (80 mL). The mixture was heated under reflux for 5 h (monitored by TLC) and the resulting solution was concentrated under reduced pressure and left to cool. The formed precipitate was filtered off, washed with H_2O (5 mL) and EtOH (5 mL), dried and recrystallized from EtOH to give **4** and **5** in 88–95% yields.

O-Acetylated Derivatives of Sugar Uracilylmethylhydrazones 6–7; General Procedure

A cold solution of sugar uraciloylhydrazones **4** and/or **5** (1 mmol) in anhydrous pyridine (3 mL) was treated with Ac_2O (3 mL). The reaction mixture was stirred overnight then poured onto crushed ice (10 g). The separated product was filtered off, washed with H_2O (5 mL), dried and crystallized from EtOH–H_2O (20 mL, 1:1), to afford **6** and **7** in 95–99% yields.

Table 3 Physicochemical Data of New Compounds

Compd	Mp (°C)[a]	$[\alpha]_D^{20}$(*c* 1, DMSO)	Mol formula (mol wt)	Yield (%)	Analysis (%, Calcd/Found)		
					C	H	N
2a	111–113	–	$C_8H_{10}N_2O_4$ (198.17)	85	48.22/ 48.20	5.09/ 4.97	14.14/ 14.07
2b	135–137	–	$C_9H_{12}N_2O_4$ (212.20)	89	50.94/ 50.88	5.70/ 5.61	13.20/ 13.09
3a	202–204	–	$C_6H_8N_4O_3$ (184.15)	90	39.13/ 38.97	4.38/ 4.27	30.42/ 30.33
3b	193–195	–	$C_7H_{10}N_4O_3$ (198.18)	93	42.42/ 42.22	5.09/ 4.98	28.27/ 28.13
4a	145–147	–4.1	$C_{11}H_{16}N_4O_7$ (317.26)	93	41.77/ 41.56	5.10/ 5.04	17.72/ 17.67
4b	150–152	+30.1	$C_{11}H_{16}N_4O_7$ (317.26)	92	41.77/ 41.61	5.10/ 5.02	17.72/ 17.69
4c	188–190	+5.2	$C_{12}H_{18}N_4O_8$ (346.29)	90	41.62/ 41.50	5.24/ 5.17	16.18/ 16.07
4d	177–179	+22.7	$C_{12}H_{18}N_4O_8$ (346.29)	88	41.62/ 41.43	5.24/ 5.13	16.18/ 16.02
5a	160–161	–12.5	$C_{12}H_{18}N_4O_7$ (330.29)	92	43.64/ 43.51	5.49/ 5.37	16.96/ 16.77
5b	173–175	+6.4	$C_{12}H_{18}N_4O_7$ (330.29)	93	43.64/ 43.57	5.49/ 5.33	16.96/ 16.79
5c	150–152	+33.2	$C_{13}H_{20}N_4O_8$ (360.32)	95	43.33/ 43.21	5.59/ 5.43	15.55/ 15.44
5d	180–181	+12.3	$C_{13}H_{20}N_4O_8$ (360.32)	90	43.33/ 43.19	5.59/ 5.40	15.55/ 15.34
6a	130–132	–11.5	$C_{19}H_{24}N_4O_{11}$ (484.41)	95	47.11/ 47.00	4.99/ 4.88	11.57/ 11.52
6b	125–126	+63.6	$C_{19}H_{24}N_4O_{11}$ (484.41)	96	47.11/ 47.02	4.99/ 4.77	11.57/ 11.37
6c	160–162	+22.1	$C_{22}H_{28}N_4O_{13}$ (556.47)	97	47.48/ 47.42	5.07/ 5.00	10.07/ 10.01
6d	144–146	+19.2	$C_{22}H_{28}N_4O_{13}$ (556.47)	95	47.48/ 47.37	5.07/ 4.98	10.07/ 10.00
7a	140–142	–34.5	$C_{20}H_{24}N_4O_{11}$ (498.44)	95	48.19/ 48.10	5.26/ 5.21	11.24/ 11.13
7b	155–157	+12.3	$C_{20}H_{24}N_4O_{11}$ (498.44)	96	48.19/ 48.11	5.26/ 5.17	11.24/ 11.10
7c	foam	+22.9	$C_{23}H_{30}N_4O_{13}$ (570.50)	99	48.42/ 48.33	5.30/ 5.23	9.82/ 9.76
7d	foam	+28.2	$C_{23}H_{30}N_4O_{13}$ (570.50)	96	48.42/ 48.34	5.30/ 5.19	9.82/ 9.66
8c	114–115	+5.7	$C_{24}H_{30}N_4O_{14}$ (598.51)	69	48.16/ 48.00	5.05/ 4.91	9.36/ 9.19
8d	124–126	+7.6	$C_{24}H_{30}N_4O_{14}$ (598.51)	68	48.16/ 48.01	5.05/ 4.90	9.36/ 9.16
9c	129–130	+12.1	$C_{25}H_{32}N_4O_{14}$ (612.54)	71	49.02/ 48.88	5.27/ 5.07	9.15/ 9.02
9d	134–136	+19.3	$C_{25}H_{32}N_4O_{14}$ (612.54)	68	49.02/ 48.82	5.27/ 5.20	9.15/ 9.10

[a] Recrystallized from EtOH.

4-Acetyl-5-(*O*-acetylalditolyl)-2-(uracil-1-ylmethyl)-1,3,4-oxadiazolines 8–9; General Procedure

A solution of sugar uraciloylhydrazones **4** and/or **5** (1 mmol) in Ac_2O (5 mL) was refluxed for 1 h. The resulting solution was poured onto crushed ice (10 g) and the product that separated out was filtered off, washed with a sat. $HaHCO_3$ (3 × 10 mL) followed by H_2O (3 × 10 mL) and then dried well. The products were recrystallized from EtOH to afford **8** and **9** in 68–71% yields.

Preparation and Culture of Hep G2 2.2.15 Cells

The required cell line was made by transfection of Hep G2-cells with a plasmid containing multiple tandem copies of the HBV genome (subtype ayw).[12a] The 2.2.15 cell line was maintained in RPMI-1640 (Glutamax) culture media containing 100 IU/mL nystatin and 380 μg/mL G418 (geneticin). The transferred HEP G2-2.2.15 cell line was kept in tissue culture flasks with 5% CO_2 at 37 °C. Subcultures were set up after a week by aspiration of the media from culture flask and washing the cells twice with PBS. A 10% solution of versene/trypsin was added and the cells were incubated for 1 min at 37 °C.

Cytotoxicity Assay

A colorimetric assay for living cells utilized the colorless substrate 3-(3,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) that is modified to produce the colored product by any living cells, but not by dead cells or tissue culture medium. The cytotoxic effect of the compounds was accessed by culturing the Hep G2-2.2.15 cells in the presence of compounds using a MTT-assay.[12b,c]

Calculation of IC_{50} and CC_{50}

The 50% inhibitory concentration of antiviral drugs (IC_{50}) was determined by interpolation from the plots of amount of DNA copies versus antiviral drug concentration. The 50% cytotoxic effect (CC_{50}) was calculated from the average viability of the cells with concentration of drugs.[12c]

References

(1) (a) Henichart, J. P.; Houssin, R.; Berier, J. L. *J. Heterocycl. Chem.* **1986**, *23*, 1531. (b) Awad, L. F.; El Ashry, E. S. H. *Carbohydr. Res.* **1998**, *312*, 9. (c) Varvarasou, A.; Sistra-Papastaikoud, T.; Tsantili-Kakoulidou, A.; Vamvakides, A. *Farmaco* **1998**, *53*, 320. (d) Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altmok, G. *Farmaco* **2002**, *57*, 101. (e) Holla, B. S.; Poorjary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem.* **2002**, *37*, 511. (f) Amir, M.; Shikha, K. *Eur. J. Med. Chem.* **2004**, *39*, 535. (g) Demirbas, N.; Alpay Karaoglu, S.; Demirbas, A.; Sancak, K. *Eur. J. Med. Chem.* **2004**, *39*, 793.

(2) (a) Mishrah, L.; Said, M. K.; Itokawa, H.; Takeya, K. *Bioorg. Med. Chem.* **1995**, *3*, 1241. (b) Ateş, O.; Kocabalkanli, A.; Cesur, N.; Otuk, G. *Farmaco* **1998**, *53*, 541. (c) Kocabalkanli, A.; Ateş, O.; Otuk, G. *Farmaco* **2001**, *56*, 975. (d) Sahin, G.; Palaska, E.; Ekizoglu, M.; Özalp, M. *Farmaco* **2002**, *57*, 530. (e) Küçükgüzel, Ş. G.; Oruç, E. E.; Rollas, S.; Şahin, F.; Özbek, A. *Eur. J. Med. Chem.* **2002**, *37*, 187. (f) Demirbas, N. *Turk. J. Chem.* **2005**, *29*, 125.

(3) El-Emam, A. A.; Al-Deep, A. O.; Al-Omar, M.; Lehmann, J. *Bioorg. Med. Chem.* **2004**, *12*, 5107.

(4) Hassan Khan, M. T.; Choudhary, M. I.; Mohammed Khan, K.; Rani, M.; Rahman, A. *Bioorg. Med. Chem.* **2005**, *13*, 3385.

(5) (a) Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G. *J. Med. Chem.* **1977**, *20*, 256. (b) Markar, G. M.; Keseru, G. M. *J. Med. Chem.* **1997**, *40*, 4154.

(6) (a) Srivastava, P. C.; Robins, R. K. *J. Med. Chem.* **1983**, *26*, 445. (b) Franchetti, P.; Cappellacci, L.; AbuSheikha, G.; Jayaram, H. N. *J. Med. Chem.* **1997**, *40*, 1731.

(7) (a) Petrie, C. R.; Revankar, G. R.; Dalley, N. K.; George, R. D. *J. Med. Chem.* **1986**, *29*, 268. (b) Hammerschmidt, F.; Peric, B.; Ohler, E. *Monatsh. Chem.* **1997**, *128*, 183.

(8) (a) El Ashry, E. S. H.; El Kilany, Y. *Acyclonucleosides: Part 1,* In *Advances in Heterocyclic Chemistry*, Vol. 67; Katritzky, A. R., Ed.; Academic Press: New York, **1996**, 391. (b) El Ashry, E. S. H.; El Kilany, Y. *Acyclonucleosides: Part 2,* In *Advances in Heterocyclic Chemistry*, Vol. 68; Katritzky, A. R., Ed.; Academic Press: New York, **1997**, 1. (c) El Ashry, E. S. H.; El Kilany, Y. *Acyclonucleosides: Part 3,* In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, **1998**, Vol. 69; 129.

(9) El-Essawy, F. A.; Khattab, A. F.; Abdel-Rahman, A. A.-H. *Monatsh. Chem.,* in press.

(10) (a) Rashed, N.; Shoukry, M.; El Ashry, E. S. H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 149. (b) El Ashry, E. S. H.; Abdul-Ghani, M. M. *Nucleosides, Nucleotides* **2004**, *23*, 567. (c) Mousaad, A.; Rashed, N.; Ramadan, E.; El Ashry, E. S. H. *Spectrosc. Lett.* **1994**, *1*, 677. (d) Abdel-Aal, M. T.; El-Sayed, W. A.; El Ashry, E. S. H. *Arch. Pharm. Chem. Life Sci.* **2006**, *339*, 656.

(11) (a) El Ashry, E. S. H.; Nassr, M.; Abdel Rahman, M. A.; Rashed, N.; Mackawy, K. *Carbohydr. Res.* **1980**, *82*, 149. (b) El Ashry, E. S. H.; Rashed, N.; Mousaad, A. *Carbohydr. Res.* **1998**, *100*, 39.

(12) (a) Sells, M. A.; Zelent, A. Z.; Shvartsman, M.; Acs, G. *J. Virol.* **1988**, *62*, 2836. (b) Korba, B. E.; Gerin, J. L. *Antiviral. Res.* **1992**, *19*, 55. (c) Fouad, T.; Nielsen, C.; Brunn, L.; Pederson, E. B. *J. Azhar Med. Facul. (GIRLS)* **1998**, *19*, 1173.

(13) Doong, S. L.; Tsai, C. H.; Schinazi, R. F.; Liotta, D. C.; Cheng, Y. C. *Proc. Nat. Acad. Sci. U.S.A.* **1991**, *88*, 4895.